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**Mini review article**

# Human herpesvirus-6 and the etiology of multiple sclerosis: a literature review

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***Background:*** There is no consensus in the literature on the role of human herpes virus-6 (HHV-6) in multiple sclerosis (MS) onset or progression.
***Objective:*** We evaluated a possible role for HHV-6 in MS onset and progression.
***Methods:*** We conducted a literature search of PubMed and Google scholar with the following search terms: ("multiple sclerosis" OR "MS") and ("Human Herpes Virus-6" OR "HHV-6").
***Results:*** A total 21 publications were retrieved, of which 19 case-control studies were included. A further 25 articles were retrieved for background information.
***Conclusion:*** There was insufficient evidence to support a role of HHV-6 in MS onset and progression.

***Keywords:*** Etiology, human herpes virus-6, multiple sclerosis, review

There is no consensus in the literature on the role of human herpes virus-6 (HHV-6) in multiple sclerosis (MS) onset or progression.

## Method

### *Database search*

We conducted a literature search of PubMed and Google scholar with the following search terms: ("multiple sclerosis" or "MS") and ("Human Herpes Virus-6" or "HHV-6"). In total 21 publications were retrieved (**Figure 1**) of which 19 articles had results for cases and controls, 2 articles were excluded; 1 article had results for cases only and 1 article had results for HHV-6A only. A further 25 articles were retrieved for background information. Full text was available for all of the articles used.

### *Criteria for the selection and extraction of results*

Because of the relative scarcity of publications regarding HHV-6 presence and/or expression in the disease etiology of MS (**Table 1**), our literature search was not limited by date or publication, different populations, MS disease status, different specimen type, or virus detection method.

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### *Inclusion criteria*

1. Articles regarding the presence and/or expression of HHV-6 reported for patients with MS, both in remission and with active disease, healthy controls as well as for patients with other neurological disorders (OND).

2. The presence of HHV-6 double-stranded DNA as measured against viral DNA detected within intracellular tissue, and expression as measured against viral RNA detected in intracellular tissue or viral DNA in extracellular tissue, the last two conditions denoting active infection.

3. Methods used included polymerase chain reaction (PCR) assays, used for the molecular amplification of viral DNA or cDNA converted RNA and immunohistochemistry for the detection of protein synthesis.

### *Exclusion criteria*

1. Articles without results for HHV-6 presence and/or expression for both cases and controls.

2. Articles without results for both HHV-6 A or B.

## Results and discussion

In general, after primary infection herpesviruses establish a latent infection with subsequent periodic reactivation. They have been reported to establish

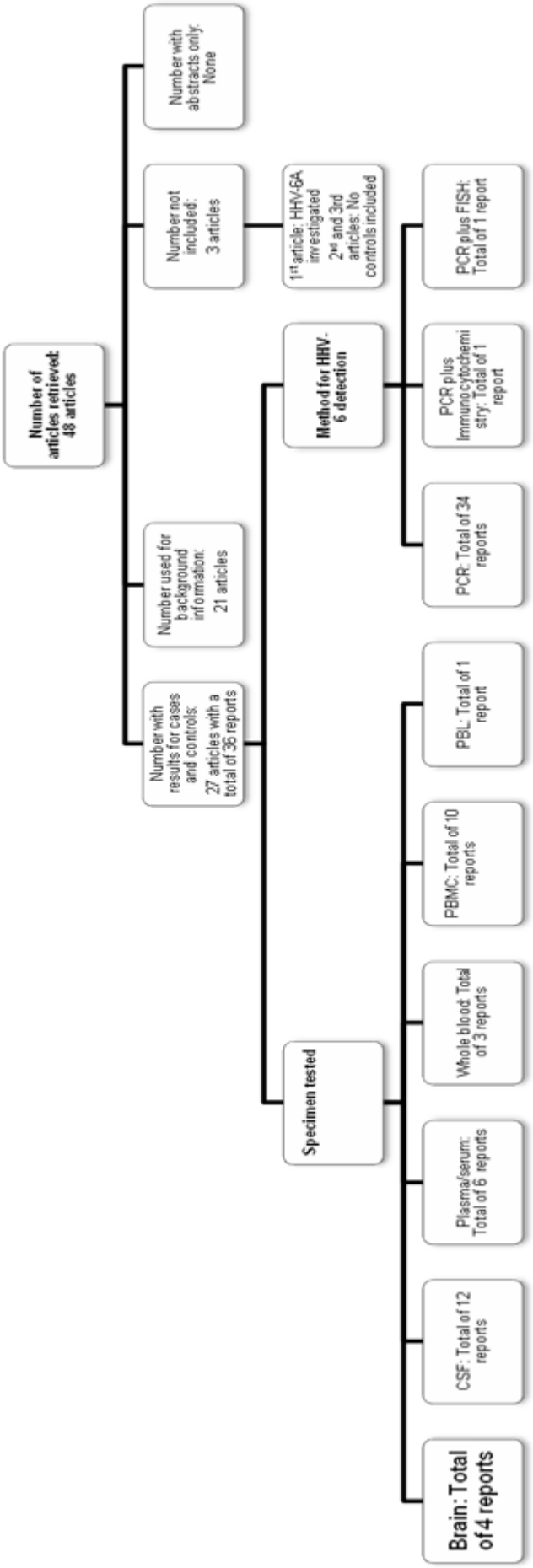


**Figure 1.** The articles retrieved and selected for the current review on human herpes virus-6 in patients with multiple sclerosis and control subjects. HHV-6 = human herpes virus-6, PCR = polymerase chain reaction, CSF = cerebrospinal fluid, FISH = fluorescence in situ hybridization, PBMCs = peripheral blood mononuclear cells, PBLs = peripheral blood mononuclear leukocytes

**Table 1.** Summary of information from articles reviewed and selected for results on human herpes virus-6 in patients with multiple sclerosis and control subjects

| Authors | Study design | Population studied | Sample size: total and patients with MS | Specimen tested | Method for HHV-6 detection | Outcome; HHV-6 prevalence (expression) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patients with MS | Healthy controls | Non-MS controls | OND |
| Challoner et al. [3] | Not stated | Los Angeles and Seattle | N,86; N,32 | Brain | Nested PCR/viral DNA (in text: immunocytochemistry) | 78.0% | | 74% | |
| Sanders et al. [11] | Not stated | Not stated | N,74; N,37 | Brain | PCR/viral DNA | 57% | | 43% | |
| Opsahl and Kennedy [13] | Not stated | Not stated | N,21; N,16 | Brain | Nested PCR/viral DNA (in text: FISH/RNA) | 100% | 100% | | |
| Mameli et al. [39] | Not stated | Not stated | N,15; N,5 | Brain | Quantitative real-time PCR/viral RNA | CPMS (0/5; 0%) | (1/4; 25%) | | (1/6; 16.7%) |
| Martin et al. [19] | Not stated | Stockholm and Goteborg | N,46; N,26 | CSF | Nested PCR/viral DNA | 0% | | | 0% |
| Enbom et al. [1] | Retrospective | Stockholm, Sweden | N,68; N,51 | CSF | PCR/viral DNA | 5.9% | | | 5.9% |
| Taus et al. [12] | Not stated | Not stated | N,34; N,25 | CSF | PCR/viral DNA | RRMS (Remission and active): 0% | | | 0% |
| Mancuso et al. [2] | Not stated | Milan, Italy | N,85; N,38 | CSF | Nested PCR/viral DNA | RRMS: 8.7%, CPMS: 6.7% | | | 7.1% |
| Alvarez-Lafuenteet al. [21] | Not stated | Not stated | N,92; N,48 | CSF | Quantitative real-time PCR/viral DNA | RRMS: 10.4% | | | 0% |
| Ahram et al. [26] | Not stated | Jordan | N,8; N,5 | CSF | Nested PCR/viral DNA | 75.0% | | | 68% |
| Franciotta et al. [20] | Not stated | Not stated | N,79; N,54 | CSF | Real-time PCR/viral DNA | 0% | | | 0% |
| Mancuso et al. [22] | Not stated | Milan, Italy | N,81; N,51 | CSF | Real-time PCR/viral DNA | 1.9% | | | 0% |
| Gustafsson et al. [48] | Not stated | Sweden | N82, N27 | CSF | Nested PCR/Viral DNA | Possible MS: 3.7% | | Non-MS controls: 0% | OND: GBS: 0% CIDP: 0% |
| Mechelli et al. [25] | Not stated | Not stated | N159, N60 | CSF | PCR | (1/60, 1.7%) | | | OIND: (4/48, 8.3%) NIND: (1/51, 2%) |
| Sotelo et al. [23] | Not stated | Mexico | N74, N53 | CSF | Real-Time PCR/Viral DNA | MS: Remission: 0% Active: 4%, Progressive: 0% | | | 0% |
| van Nierop et al. [24] | Not stated | Netherlands | N109, N53 | CSF | Real-time PCR /Viral DNA | 0% | | | (1/56, 1.8%) |
| Martin et al. [19] | Not stated | Stockholm and | N,46; N,26 | Serum | Nested PCR/viral DNA | 0% | | | 0% |
| Alvarez-Lafuente et al. [31] | Not stated; | Madrid, Spain Goteborg | N,149; N,103 | Serum | Quantitative real-time PCR/viral DNA | RRMS: 14.6% | 0% | | |
| Ahram et al. [26] | Not stated | Jordan | N,71; N,34 | Serum | Nested PCR/viral DNA | RRMS: 24%, SPMS: 40%, PRMS: 0% | 20% | | 67% |

**Table 1.** Summary of information from articles reviewed and selected for results on human herpes virus-6 in patients with multiple sclerosis and control subjects (Continue)

| Authors | Study design | Population studied | Sample size: total and patients with MS | Specimen tested | Method for HHV-6 detection | Outcome; HHV-6 prevalence (expression) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patients with MS | Healthy controls | Non-MS controls | OND |
| Franciotta et al. [20] | Not stated | Not stated | N,79; N,54 | Serum | Real-time PCR/viral DNA | 0% | | | 0% |
| Behzad-Behbahani et al. [32] | Prospective | Iran | N70, N,30 | Serum | Nested PCR/viral DNA | 33% | 5% | | 5% |
| Gustafsson et al. [48] | Not stated | Sweden | N263, N208 | Plasma/ serum | Nested PCR/Viral DNA | Possible MS: 7.4% (plasma) IFN□ treated MS: NAb+: 3.8% NAb–: 1.0% (serum) | | Non-MS controls: 0% (plasma) | OND: GBS: 7.1% CIDP: 12.5% (serum) |
| Hay and Tenser, [35] | Not stated | Not stated | N,36; N,29 | PBLs | PCR/viral DNA | RRMS: 6% SPMS: 8% | 14% | | |
| Ablashi et al. [41] | Not stated | United States of America | N,104; N,21 | PBMCs | PCR/viral DNA | Remission: 66.7%; Active: 80.0% | 60.0% | | 60.0% |
| Taus et al. [12] | Not stated | Not stated | N,23; N,14 | PBMCs | PCR/viral DNA | RRMS (Remission and active): 2/14; 14.3% | | | 0% |
| Alvarez-Lafuente et al. [31] | Not stated | Madrid, Spain | N,149; N,103 | PBMCs | Quantitative real-time PCR/viral DNA | RRMS: 53.4% | 30.4% | | |
| □lvarez-Lafuente et al. [40] | Not stated | Madrid, Spain | N,204; N,102 | PBMCs | Nested PCR/viral DNA | RRMS with β-interferon treatment: 48.4%, without: 50.0% | 21.6% | | |
| Chapenko et al. [30] | Not stated | Not stated | N,197; N,26 | PBMCs | PCR/viral DNA | RRMS: 63.6%; SPMS: 60.0% | 28.7% | | 28.6% |
| Alvarez-Lafuente et al. [43] | Case-control study | Madrid, Spain | N,154; N,105 | PBMCs | Quantitative real-time reverse transcription PCR/multiple genes/viral mRNA | RRMS: (16%) | (0%) | | |
| Mameli et al. [39] | Not stated | Not stated | N,49; N,35 | PBMCs | Quantitative real-time PCR/viral DNA | 34.3% | 21.4% | | |
| Mameli et al. [39] | Not stated | Not stated | N,49; N,35 | PBMCs | Quantitative real-time PCR PCR/viral RNA | (1/35; 2.9%) | (0/14; 0%) | | |
| Sotelo et al. [36] | Not stated | Not stated | N,296; N,171 | PBMCs | PCR/viral DNA | RRMS Remission: 2% Active: 23%, Progressive: 0% | 0% | | 0% |

**Table 1.** Summary of information from articles reviewed and selected for results on human herpes virus-6 in patients with multiple sclerosis and control subjects (Continue)

| Authors | Study design | Population studied | Sample size: total and patients with MS | Specimen tested | Method for HHV-6 detection | Outcome; HHV-6 prevalence (expression) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patients with MS | Healthy controls | Non-MS controls | OND |
| Fredj et al. [38] | Not stated | Monastir, Tunisia | N,51; N,51 | Whole blood | Nested PCR/viral DNA | RRMS Remission; 6.1%; Active: 5.6% | 2.0% | | |
| Ben-Fredj et al. [42] | Not stated | Tunisia | N123, N,68 | Whole blood | Quantitative real-time PCR/viral DNA | 6.7% | 3.2% | | |
| Hon et al. [37] | Not stated | South Africa | N61, N31 | Whole blood | PCR | 3.2% | 0% | | |

MS = multiple sclerosis, OND = other neurological disorders, HHV-6 = human herpes virus-6, PCR = polymerase chain reaction, CPMS = chronic progressive MS, DNA = deoxyribonucleic acid, FISH = fluorescence in situ hybridization, CSF = cerebrospinal fluid, RRMS = relapsing remitting MS, PRMS = primary progressive MS, OIND = other inflammatory diseases, NIND = other noninflammatory diseases; PBML = peripheral blood mononuclear leukocytes, NAb+ = patients with neutralizing antibodies, NAb– = patients without neutralizing antibodies, GBS = Guillain–Barre syndrome, CIDP = chronic inflammatory demyelinating polyradiculoneuropathy, SPMS = secondary progressive MS, PBMCs = peripheral blood mononuclear cells

latency in lymphocytes and nerve ganglia and have shown the capacity to induce demyelination, such as has been reported in patients with MS [1, 10-12]. However, these viruses have also been reported in healthy control subjects and in patients with other neurological disorders (OND), and as such their role as causative agent for MS onset and progression has not been elucidated. In this regard, reports show similar results for HHV-6 presence (DNA) in patients with MS and control subjects. Challoner et al. [3] reported HHV-6 DNA present in brain tissue from 78% of patients with MS, but also in 74% of non-MS controls. Similarly, Sanders et al. [11] reported HHV-6 DNA present in brain tissue in 57% of patients with MS and in 43% of non-MS controls, including patients with OND and nonneurological diseases (NND). Viral RNA expression was reported restricted to oligodendrocytes for both patients with MS and normal control brains [13], with localization of HHV-6 protein shown in oligodendrocytes from patients with MS, but absent in oligodendrocytes from non-MS controls[3]. However, Challoner et al. [3] also observed HHV-6 antigens in neurons, astrocytes, and macrophages from patients with MS and in certain non-MS controls. Glial cells (oligodendrocytes, microglia and astrocytes) are responsible for the survival of neurons [14-16] and virus presence in these cells could contribute to inflammatory activation. However, this seems unlikely to be the cause of the disease because this condition has also been reported in control brains, which did not result in MS per se. Current reports therefore fail to show the consistent presence of HHV-6 in brain tissue from patients with MS and furthermore have also reported its presence at high prevalence rates in control subjects, which confirms that HHV-6 is a commensal virus of the human brain [3, 17]. However, the presence of the virus may well contribute to existing damage and as such it would be of interest to investigate a possible association between viral presence and the degree of damage to the CNS, which may be vast. In this regard, G□pfert et al. [18] reported the myelin yield from "normal"-appearing white matter from patients with MS to be two-thirds of that of age-matched control brains.

These reports are also confirmed by findings of viral presence in the cerebrospinal fluid (CSF), which has been used as a marker for viral replication within the central nervous system (CNS) [2]. As can be expected, healthy controls did not contribute to CSF sampling, but reports for both patients with MS and OND showed very few HHV-6 DNA positive cases. Martin et al. [19], Taus et al. [12], and Franciotta et al. [20] reported that HHV-6 DNA was absent in the CSF from patients with MS and patients with OND. □lvarez-Lafuenteet al. [21], Mancuso et al. [22], and Sotelo et al. [23] reported HHV-6 DNA in the CSF from 10.4%, 1.9%, and 4% of patients with MS respectively and none in patients with OND. In this regard, Taus et al. [12], □lvarez-Lafuente et al. [21], and Sotelo et al. [23] reported on patients with MS with active disease included. van Nierop et al. [24] reported HHV-6 DNA was absent in the CSF from patients with MS and present in 1.8% of patients with OND. Enbom et al. [1] reported HHV-6 DNA in the CSF of 5.9% of both patients with MS and with OND and Mechelli et al. [25] in 1.7% of patients with MS, in 8.3% of patients with other inflammatory diseases (OIND), and in 2% of patients with other noninflammatory diseases (NIND). Where higher prevalence was reported, such as in the report by Ahram et al. [26], who reported HHV-6 DNA in CSF of 75% of patients with MS from Jordan, similarly high prevalence (68%) was reported for patients with OND. Similar low numbers were reported for patients with different types of MS. In this regard, about 80% of patients with MS were diagnosed with relapsing-remitting MS (RRMS), when periods of active disease may be followed by periods of remission of the disease. Of these, up to 90% will progress to secondary progressive MS (SPMS), with minor or no remission of the disease [reviewed 27-28]. Mancuso et al. [2] reported HHV-6 DNA in the CSF from 8.7% of patients with RRMS, in 6.7% of chronic progressive MS (CPMS) and in 7.1% of patients with OND. In a later study, Mancuso et al. [22] reported even lower numbers, in 1.9% of patients with MS (including RRMS, chronic progressive MS, and clinically isolated syndrome), with none of the patients undergoing immunosuppressive or immunomodulating therapy. HHV-6 replication in the CSF therefore did not show any association with either the type of MS or the disease status in patients with MS and therefore does not support a role for the virus in the MS disease etiology.

The presence of viral DNA in serum/plasma has been used as a marker for active viral infection [29-30]. The herpesviruses have DNA genomes and because they need to infect cells for replication, extracellular viral DNA most probably denotes assembled virions, liberated from cells for further

infection. Martin et al. [19] reported HHV-6 DNA absent in the serum from both patients with MS and with OND. Similarly, Franciotta et al. [20] reported HHV-6 DNA absent in serum from patients with MS in remission, with active disease, in healthy controls and in patients with OND. Alvarez-Lafuenteet al. [31] reported HHV-6 DNA in serum of 14.6% of patients with RRMS, with no difference between active and remission stages of the disease and absent in serum of healthy controls. Both Behzad-Behbahani et al. [32] and Ahram et al. [26] reported higher prevalence of HHV-6 DNA in serum from patients with MS; Behzad-Behbahani et al. [32] reported HHV-6 DNA in serum from 33% of patients with MS, in 5% of healthy controls, and in 5% of patients with OND. By contrast, Ahram et al. [26] also reported a high prevalence rate for patients with OND; the authors reported HHV-6 DNA in serum of 24% of patients with RRMS, in 40% of patients with secondary progressive MS (SPMS), absent in patients with primary progressive MS (PRMS), but also present in 20% of healthy controls and in 67% of patients with OND. HHV-6 is known to affect several mediators of the immune system [4] and to cause infectious diseases in immunocompromised patients [33]. However, these reports suggest that HHV-6 reactivation may be sufficiently suppressed in healthy control subjects and in patients with OND, but that a subgroup of patients with MS may not do this effectively. Nevertheless, this reactivation was not related to the active and remission stages of the disease as measured against the above mentioned report from Alvarez-Lafuenteet al. [31]. Therefore, although these reports are too few for any conclusive evaluation, it is possible that reactivation of HHV-6 in patients with MS may be the result of abnormalities in the immune response, rather than a cause of the disease, and in this regard various abnormalities have been reported in the immune responses from patients with MS [4].

The presence of peripheral blood leucocytes has been reported in brain tissue from patients with MS, including the presence of lymphocytes around small blood vessels [7, 34], and therefore viral presence in these cells could be contributing to the disease pathology, either as contributors to brain infection when recruited or by rendering the cells incapable of performing their immunological role. In this regard, HHV-6 has also been associated with T-lymphocytes [17, 35]. Reports on the presence of HHV-6 DNA in peripheral blood mononuclear cells (PBMCs) or peripheral blood from healthy controls vary considerably. Sotelo et al. [36] and Hon et al. [37] reported HHV-6 DNA absent, Fredj et al. [38] in 2.0%, Hay and Tenser, [35] in 14%, and Mameli et al. [39] in 21.4% of healthy controls. □lvarez-Lafuente et al. [31], Alvarez-Lafuenteet al. [40], and Chapenko et al. [30] reported higher prevalence rates, 30.4%, 21.6%, and 28.7% respectively, while Ablashi et al. [41] reported HHV-6 DNA in PBMCs from 60.0% of healthy controls. These reports show that HHV-6 may establish latency also in healthy subjects and with rather a wide prevalence range, 0% to 60.0% depending on the study population. Prevalence of the herpesvirus as measured against viral DNA presence was not as high as the 90% seroprevalence reported for herpes viruses in humans [33]. Similar results have been reported for HHV-6 DNA in PBMCs from patients with MS as for healthy controls. Fredj et al. [38] reported HHV-6 DNA in peripheral blood samples from 6.1% of patients with RRMS in remission and in 2.0% of healthy controls and Sotelo et al. [36] in PBMCs from 2% of patients with RRMS in remission and in none of the healthy controls. Ben-Fredj et al. [42] reported HHV-6 DNA in whole blood from 6.7% of patients with MS from Tunisia and in 3.2% of healthy controls and Hon et al. [37] in 3.2% of patients with MS from South Africa and absent in healthy controls. Ablashi et al. [41] reported higher prevalence rates; the authors reported viral DNA in PBMCs from 66.7% of patients with MS in remission, but also in 60.0% of healthy controls, and therefore equally higher for both patients and controls. These reports suggest that a baseline prevalence of HHV-6 in the population may have had an effect on that manifested in patients with MS.

A comparison of cases of MS in remission and with active disease does not support a contributing role for the virus in disease activation. Fredj et al. [38] reported HHV-6 DNA in peripheral blood samples from 5.6% of patients with RRMS with active disease and similar results, 6.1% for patients in remission. Ablashi et al. [41] reported HHV-6 DNA in PBMCs from 80.0% of patients with MS with active disease, but also in 66.7% of patients with MS in remission, and Sotelo et al. [36] similarly in 23% of patients with active disease and in 2% of patients in remission. The reports by Ablashi et al. [41] and Sotelo et al. [36] suggest that the percentage of cases presenting with HHV-6 DNA during active disease may be

a representation of baseline values in patients. Furthermore, although more patients presented with HHV-6 DNA during active disease, some did not, and especially in the study by Sotelo et al. [36] and Fredj et al. [38], the majority did not, which makes the presence of HHV-6 DNA in PBMCs an unlikely trigger for MS relapses. Recent reports from a study by Sotelo et al. [23] confirmed these findings, the authors reported HHV-6 DNA absent in PBMCs from patients with MS in remission, with active disease, with progressive MS as well as in patients with OND.

Patients with OND seem to experience lower prevalence rates for HHV-6 presence than patients with MS, but again prevalence varies accordingly. Sotelo et al. [36] reported HHV-6 DNA in PBMCs from 23% of patients with MS with active disease, in 2% of patients with MS in remission and absent in patients with OND. Taus et al. [12] reported HHV-6 DNA in PBMCs from 2 of 14 patients with MS and absent in patients with OND. By contrast, Ablashi et al. [41] reported HHV-6 DNA in PBMCs of 80.0% of patients with MS with active disease, in 66.7% of patients with MS in remission, but also in 60.0% of patients with OND. These reports suggest that in a population with high HHV-6 DNA prevalence in patients with MS, a similar high prevalence was reported in patients with OND, and vice versa. Furthermore, replicating HHV-6 has not been reported in PBMCs from a high number of patients with MS and similarly also not in many healthy controls. Mameli et al. [39] reported HHV-6 RNA in PBMCs from 1 of 35 patients with MS with active disease and absent in PBMCs from healthy controls. lvarez-Lafuente et al. [43] investigated different HHV-6 genes and reported active HHV-6 infection (mRNA) in PBMCs of 16% of patients with MS (32/105 with active disease) and absent in PBMCs from healthy controls. These findings fail to suggest a causative role for HHV-6 DNA in PBLs/PBMCs in the MS disease etiology, but rather that the slightly higher prevalence in patients with MS as compared with that of OND, may be an inability of patients with MS to eliminate initial infection to the same degree as patients with various OND can. Reports also failed to demonstrate a causative role for HHV-6 replication in immune cells in the MS disease etiology. This seems to be confirmed by reports on HHV-6 presence in PBMCs from patients with different stages of MS; Chapenko et al. [30] reported similar prevalence rates for HHV-6 in PBMCs from patients with RRMS and SPMS, 63.6% and 60.0% respectively, while Hay and Tenser, [35] reported much lower prevalence rates, but similarly lower for both types of MS, in 6% of patients with RRMS and in 8% of patients with SPMS. These findings do not support a role for HHV-6 DNA presence in PBMCs as either causative for the disease onset or progression from RRMS to SPMS.

There is a scarcity of information regarding the association between the herpesviruses and the different aspects of the immune response, including inflammation in patients with MS. Treatment of MS includes antiviral and antiinflammatory/ immunosuppressive medication, which highlights the need for clarification of the role that the viruses may play in inflammatory activation in these patients. In this regard, Alvarez-Lafuenteet al. [40] reported similar prevalence of HHV-6 DNA in PBMCs from patients with RRMS, with and without β-interferon treatment, 48.4% and 50.0% respectively. Similarly, but at a lower prevalence, Fredj et al. [38] reported HHV-6 DNA in peripheral blood samples from 8% of patients with RRMS, treated with β-interferon and in 3.8% of patients with RRMS, not treated with β-interferon. β-Interferon is an immunomodulatory drug [44], which has been approved for the treatment of MS as it decreases the clinical relapse rate and disease activity and severity [28, 45, 46]. Taken together, these reports do not support a causative role for HHV-6 DNA in PBMCs from patients with MS in the disease status or progression. Furthermore, it shows that β-interferon treatment plays no role in the prevalence of HHV-6 in patients with MS. There is scarcity of literature regarding the association between viral presence and measurements of disease progression such as MRI, or measures of symptoms such as the Kurtzke Expanded Disability Status Scale [47] and measures of inflammation/infection such as C-reactive protein, and that may when investigated, clarify the role of this herpesvirus as a possible contributor to, albeit not cause of the disease etiology.

Current reports may not be sufficient in number to ensure unbiased findings, especially because of the wide variety in the different variables investigated. Following the above, reproducibility testing may be limited because of small numbers of publications and particularly because no date limitation could be used for the database search. Differences in age, sex, race, and ethnicity between studies may have biased reported findings. A very small number of the retrieved articles

contained stated study designs, which contributed to difficulty in the investigation of HHV-6 as a causative agent in the MS disease etiology.

## Conclusion

We concluded that reports on the role of herpes virus HHV-6 playing an etiology in MS do not support a role for this virus in the onset or progression of MS. Similarities in reports for viral presence/expression in healthy controls and patients with MS suggest that findings in patients with MS may be a reflections of specific populations/ethnicities rather than MS-specific. Where higher numbers of patients were affected than controls, some patients still remained unaffected, which suggests that patients with MS may be unable to suppress virus activation/reactivation to the same extent as patients with OND or healthy controls can. These reports therefore suggest that abnormalities may be present in the immune response and/or that an underlying problem may be present that may prevent normal immune function/response in some of these patients.

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